

PTO/38/68 (11-86)

Approved for use through 10/31/99. OMB 0651-0031

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

In re Application of

Application Number

Filed

07/566977 8/13/90

Group Art Unit

Examiner

Paper No. 16

Assistant Commissioner for Patents  
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE:

(A) referred to in United States Patent Number 5,623,065 column

(B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. filed on page of paper number

(C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. filed or

(D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

---

---

---

S.R.S.

Signature

Typed or printed name

8/14/01

Date

FOR PTO USE ONLY

Approved by:

(initials)

Unit:



US005623065A

6860

**United States Patent** [19]

Cook et al.

[11] **Patent Number:** 5,623,065[45] **Date of Patent:** Apr. 22, 1997[54] **GAPPED 2' MODIFIED OLIGONUCLEOTIDES**[75] Inventors: **Phillip D. Cook**, Vista; **Brett P. Monia**, Carlsbad, both of Calif.[73] Assignee: **Isis Pharmaceuticals, Inc.**, Carlsbad, Calif.[21] Appl. No.: **244,993**[22] PCT Filed: **Dec. 23, 1992**[86] PCT No.: **PCT/US92/11339**§ 371 Date: **Jun. 21, 1994**§ 102(e) Date: **Jun. 21, 1994**[87] PCT Pub. No.: **WO93/11339**PCT Pub. Date: **Jul. 8, 1993****Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 814,961, Dec. 24, 1991, abandoned, and Ser. No. 566,977, Aug. 13, 1990, abandoned.

[51] Int. Cl.<sup>6</sup> ..... **C07H 21/00; C07H 21/02; C07H 21/04**[52] U.S. Cl. .... **536/23.1; 536/23.2; 536/23.5; 536/23.51; 536/23.52; 536/23.53; 536/25.1; 536/25.2; 435/91.1; 435/91.2; 435/91.5; 935/6; 935/9; 935/10**[58] Field of Search ..... **514/44; 536/23.1; 536/23.2; 23.5; 23.51; 23.52; 23.53; 25.1; 25.2; 435/91.1; 91.2; 91.4; 91.5; 935/9; 6, 10**[56] **References Cited****U.S. PATENT DOCUMENTS**

4,867,187	9/1989	Duck .....	435/6
4,908,307	3/1990	Rodland et al. ....	435/6
5,013,830	5/1991	Ohtsuka et al. ....	536/25.1
5,034,506	7/1991	Summerton et al. ....	528/391
5,134,066	7/1992	Rogers et al. ....	435/91.3
5,149,797	9/1992	Pederson et al. ....	536/23.1
5,220,007	6/1993	Pederson et al. ....	536/23.1
5,256,775	10/1993	Froehler .....	536/25.6
5,366,878	11/1994	Pederson et al. ....	435/91.3
5,403,711	4/1995	Walder et al. ....	435/6
5,466,786	11/1995	Buhr et al. ....	536/26.26

**FOREIGN PATENT DOCUMENTS**

2017369	11/1990	Canada .
260032	8/1987	European Pat. Off. .
365627B1	3/1989	European Pat. Off. .
0339842	4/1989	European Pat. Off. .
0339330	11/1990	European Pat. Off. .
3915462	9/1990	Germany .
4110085	10/1992	Germany .
3-240795	of 1991	Japan .
89/05358	6/1989	WIPO .
WO90/15814	6/1990	WIPO .
WO91/06556	10/1990	WIPO .
WO91/15499	4/1991	WIPO .
WO91/12323	8/1991	WIPO .
WO94/02498	2/1994	WIPO .
WO92/07065	9/1994	WIPO .

**OTHER PUBLICATIONS**

Block et al. 1988 Gene 72, 349-360.

Cormier et al. 1988 Nuc. Acids Res. 16(10), 4583-4594.

Uhlmann et al. 1990 Chemical Reviews 90(4), 544-584.

Ikehara et al. 1977 Nuc. Acids Res. 4(12): 4249-4260.

Berkowitz et al. 1973 J. Medicinal Chemistry, 16(2): 813-814.

Kawasaki et al. 1991 (Jan.) "Synthesis and Biophysical Studies of 2'-dRIBO-F Modified Oligonucleotides", Conference on Nucleic Acid Therapeutics, Clearwater, FL.

Agrawal, S. et al., "Oligodeoxynucleoside Phosphoramidates and Phosphorothioates as Inhibitors of Human Immunodeficiency Virus" *Proc. Natl. Acad. Sci. USA* 1988 85, 7079-7083.Augustyns, et. al., "Influence of the Incorporation of (S)-9-(3,4-dihydroxy-butyl)Adenine on the Enzymatic Stability and Base-Pairing Properties of Oligodeoxynucleotides" *Nucleic Acids Research* 1991, 19, 2587-2593.Beaton, et. al., Chapter 5, Synthesis of oligonucleotide phosphorodithioates, p. 109, *Oligonucleotides and Analogs, A Practical Approach*, Eckstein, F., Ed.; The Practical Approach Series, IRL Press, New York, 1991, pp. 109-135.Borthwick, et al., "Synthesis of Chiral Carbocyclic Nucleosides" *Tetrahedron* 1992, 48, 571-623.Brill et al., "Synthesis of Deoxydinucleoside Phosphorodithioates", *J. Am. Chem. Soc.* 1991 113, 3972-3980.Cohen in *Oligonucleotides: Antisense Inhibitors of Gene Expression*, CRC Press, Inc., Boca Raton, FL (1989), pp. 1-255.Dagle et al., "Physical properties of oligonucleotides containing phosphoramidate-modified internucleoside linkages", *Nucleic Acids Research* 1991 19, 1805-1810.Dagle et al., "Targeted degradation of mRNA in *Xenopus* oocytes and embryos directed by modified oligonucleotides: studies of An2 and cyclin in embryogenesis", *Nucleic Acids Research* 1990 18, 4751-4757.Dagle et al., "Pathways of Degradation and Mechanism of Action of Antisense Oligonucleotides in *Xenopus laevis* Embryos", *Antisense Research and Development* 1991 1, 11-20.Debart et al., "Intermolecular Radical C-C Bond Formation: Synthesis of a Novel Dinucleoside Linker for Non-anionic Antisense Oligonucleosides", *Tetra. Ltrs.* 1992 33, 2645-2648.

(List continued on next page.)

**Primary Examiner**—Christopher S. F. Low  
**Attorney, Agent, or Firm**—Woodcock Washburn Kurtz Mackiewicz & Norris

[57] **ABSTRACT**

Oligonucleotides and other macromolecules are provided that have increased nuclease resistance, substituent groups for increasing binding affinity to complementary strand, and subsequences of 2'-deoxy-erythro-pentofuranosyl nucleotides that activate RNase H enzyme. Such oligonucleotides and macromolecules are useful for diagnostics and other research purposes, for modulating protein in organisms, and for the diagnosis, detection and treatment of other conditions susceptible to antisense therapeutics.